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14. ABSTRACT

Biomathematical models of fatigue and performance provide a useful methodology for the prediction of fatigue resulting from sleep loss and circadian disruption in Air Force operations. However, currently available models do not have the capability to make predictions for individual subjects, which makes them inaccurate when not applied to large groups. This project employed a cutting-edge technique called Bayesian forecasting to develop a novel biomathematical performance model to predict responses to sleep loss and circadian displacement for individual subjects. Accomplishments during the period of work covered in this report included the following: 1) mathematical derivations and parameter estimations for the implementation of the Bayesian forecasting technique in the seminal two-process model of sleep regulation and in the chronic modulating process model; 2) model validation in accordance with the Box iterative scheme of model development; and 3) construction of a biomathematical model combining the two-process model of sleep regulation with the chronic modulating process model for the effects of chronic sleep restriction. The project has been transferred and is currently being continued at Washington State University.

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EXECUTIVE SUMMARY

Biomathematical models of fatigue and performance provide a useful methodology for the prediction of fatigue resulting from sleep loss and circadian disruption in Air Force operations. However, among the most urgently needed conceptual advances in biomathematical modeling is the capability to make predictions for individual subjects, as currently available models fall short when applied to individuals. A cutting-edge technique called Bayesian forecasting, which is applied in the context of mixed-effects modeling, can provide the capability to predict responses to sleep loss and circadian displacement for individual subjects. The overall objective of this project is the development of an individualized next-generation biomathematical model of human fatigue and performance on the basis of the Bayesian forecasting technique.

Briefly, the project addresses the following specific aims: 1) Implementation of the Bayesian forecasting technique; 2) Experimental validation and model refinement; 3) Construction of a novel biomathematical model of fatigue and performance; and 4) Individualization of the novel biomathematical model of fatigue and performance. At the basis of the model development in specific aims 1 through 3 is the seminal two-process model of sleep/wake regulation, which has been used previously to predict performance, and a recently proposed chronic modulating process model that, unlike the two-process model, can account for the cumulative performance deficits resulting from chronic sleep restriction. All the elements of the project come together in the fourth specific aim, when Bayesian forecasting is implemented in the novel biomathematical model using data from experiments previously conducted in the laboratory, and the resulting individualized next-generation biomathematical model of human fatigue and performance is validated using additional data from experiments previously conducted in the laboratory.

Accomplishments during the period of work covered in this report included the following: 1) The mathematical derivations and parameter estimations for the implementation of the Bayesian forecasting technique in the seminal two-process model of sleep regulation, as used to predict performance, and in the chronic modulating process model were completed; 2) Experimental data were prepared for the first cycle of model validation and refinement, in accordance with the Box iterative scheme of model development; 3) Significant progress was made towards the construction of a biomathematical model combining the two-process model of sleep regulation with the chronic modulating process model for the effects of chronic sleep restriction; and 4) A graduate student at Drexel University completed a Master's thesis project on the topic.

This final report covers the work performed at the University of Pennsylvania for this project, which involves only the first 9 months (January 1 through September 30, 2006) of the 3 years needed to complete all the work. On October 1, 2005, the project was transferred to Washington State University, where the work continues. Once fully completed, the products of this project will include a precisely formulated method for on-line individualization of biomathematical model predictions, and implementation of this method as part of a next-generation model of performance that can then be used for the subject-specific prediction of neurobehavioral impairment that jeopardizes Air Force mission safety and success. The results of this project will be relevant also for the many operational settings in today's 24/7 society that put individuals at risk for performance deficits due to sleep loss and circadian displacement.

OBJECTIVES

Biomathematical models of fatigue and performance, based on the neurobiology of sleep/wake regulation and circadian rhythmicity, provide a useful methodology for the prediction of fatigue resulting from sleep loss and circadian disruption in Air Force operations. However, among the most urgently needed conceptual advances in biomathematical modeling is the capability to make predictions for individual subjects, as currently available models fall short when applied to individuals. No reliable predictors of inter-individual differences have been identified that could be used to tailor the existing models to individuals. In the absence of predictors, a cutting-edge technique called Bayesian forecasting, which is applied in the context of mixed-effects modeling, can still provide the capability to predict responses to sleep loss and circadian displacement for individual subjects. The overall objective of this project is the development of an individualized next-generation biomathematical model of human fatigue and performance on the basis of the Bayesian forecasting technique. This model is to combine and expand the most state-of-the-art elements of existing population-average models, and to set a new standard for prospective biomathematical modeling of neurobehavioral performance.

The project addresses the following specific aims:

1. **Implementation of the Bayesian forecasting technique.** As a first step in the development of individualized next-generation biomathematical modeling, Bayesian forecasting is implemented in the seminal two-process model of sleep regulation and in the novel chronic modulating process model for the cumulative neurobehavioral effects of chronic sleep restriction, using data from experiments previously conducted in the laboratory to turn these models into population distribution models by means of mixed-effects modeling.
2. **Experimental validation and model refinement.** Additional data from experiments previously conducted in the laboratory are used to validate and refine the individualized models developed in specific aim 1, in accordance with the Box iterative scheme of model development.
3. **Construction of a novel biomathematical model of fatigue and performance.** The most state-of-the-art elements of available biomathematical models of human fatigue and performance are combined and expanded, including the two-process model and the chronic modulating process as refined in specific aim 2, the limit-cycle oscillator model of the circadian pacemaker with a transformation previously derived by us, and a novel model for the sleep inertia effect that properly accounts for homeostatic and circadian influences.
4. **Individualization of the novel biomathematical model of fatigue and performance.** Bayesian forecasting is implemented in the novel biomathematical model of specific aim 3, using data from experiments previously conducted in the laboratory to turn this model into a population distribution model by means of mixed-effects modeling; and the resulting individualized next-generation biomathematical model of human fatigue and performance is validated using additional data from experiments previously conducted in the laboratory.

The products of this project include a precisely formulated method for on-line individualization of biomathematical model predictions, and implementation of this method as part of a next-generation model of performance that can be used for the subject-specific prediction of neurobehavioral impairment that jeopardizes Air Force mission safety and success. We plan to make the individualized next-generation biomathematical model available to the Air Force and other operational communities, and to the scientific community for further research.

COMPLETED WORK

During the first 9 months of this 3-year project, the work took place at the University of Pennsylvania. This final report describes the work done during this period, which was January 1 through September 30, 2005. A progress report for the period from January 1 until July 31, 2005 had been submitted on August 23, 2005. This final report resembles the progress report in that only two months of additional work are included. Considerable focus during those two months was on preparation for the defense and completion of the Master's thesis of Ms. Deepa Avinash, whose thesis involved a significant portion of year 1 of the project. The project is currently being continued at Washington State University, where much additional progress has been made. The latter, however, is not the focus of this final report, which deals only with the work completed at the University of Pennsylvania.

During the first 9 months of the 3-year project, considerable progress was made with respect to the specific aims of the project, as summarized below.
Specific Aim 1: Implementation of the Bayesian forecasting technique.
The mathematical/statistical derivations and parameter estimations for the implementation of the Bayesian forecasting technique in the seminal two-process model of sleep regulation, as used to predict performance, and in the chronic modulating process model were completed.
Specific Aim 2: Experimental validation and model refinement.
Experimental data were prepared for the first cycle of model validation and refinement, in accordance with the Box iterative scheme of model development.
Specific Aim 3: Construction of a novel biomathematical model of fatigue and performance.
Significant progress was made towards the construction of a biomathematical model combining the two-process model of sleep regulation with a chronic modulating process model for the effects of chronic sleep restriction.
Specific Aim 4: Individualization of the novel biomathematical model of fatigue and performance.
Work for specific aim 4 was begun in year 2 of the project (i.e., at Washington State University).

TECHNICAL RESULTS

Reformulating the two-process model
In order to prepare for, and assess the scope of the mathematical/statistical challenge of implementing the Bayesian forecasting technique in the two-process model of sleep regulation as used to predict performance, the published equations were reformulated. The published equation for the homeostatic process S during wakefulness is:

$$S_t = 1 - \exp(-\Delta t / \tau_r)\,(1 - S_{t-\Delta t}),$$

where τ_r is a time constant. Substituting S for $S - 1$ while requiring that $S < 0$ (without loss of generalizability), and replacing time constant τ_r by rate constant ρ, we get:

$$S_t = \exp(-\rho\,\Delta t)\,S_{t-\Delta t},$$

which contains a free parameter ρ, and requires an initial state $\xi = S_0$ to begin future predictions. Working out the recursiveness all the way from $t_m = t$ until $t_0 = 0$, it follows that:

$$S_t = \xi \exp(-\rho \sum_{j=1..m} \Delta t_j).$$

The published equation for the circadian process C is:

$$C_t = \sum_{k=1..5} a_k \sin(2 \pi k [t - \varphi] / \tau),$$

which contains a free parameter φ, while τ is fixed at 24h and the a_k are fixed constants.

Defining some measurable performance metric P as the dependent variable, the two-process model predicts performance as:

$$P_t = \kappa + \beta S_t + \gamma C_t,$$

where κ, β and γ are free parameters. However, β is redundant with ξ (see above) and may be dropped from the equation. Thus, predicting performance with the two-process model is essentially a 5-parameter mathematical problem: κ (baseline performance), ρ (homeostatic vulnerability), γ (circadian amplitude), ξ (prior homeostatic pressure for sleep), and φ (circadian phase). Of these 5 parameters, we consider κ, ρ and γ to be trait parameters—that is, they reflect systematic individual differences. These 3 parameters can be subjected to Bayesian forecasting (simultaneously). This finding sets the stage for the effort required for specific aim 1.

Establishing a population distribution model for the two-process model
Bayesian forecasting requires that a population distribution model be established against which measurements for an as yet unstudied individual can be referenced in order to optimize that individual's model parameters. To establish a population distribution model for performance P, as a function of free parameters κ, ξ, γ, ρ and φ, we write the model for P as a mixed-effects regression model:

$$y_{ij} = P_{ij}(\kappa_i,\rho_i,\gamma_i,\xi,\varphi) + \varepsilon_{ij} = (\kappa + \lambda_i) + S_{ij}(\rho \exp(\nu_i),\xi) + C_{ij}(\gamma \exp(\eta_i),\varphi) + \varepsilon_{ij},$$

where i is an index for the individual subjects, and j denotes time t_j (which is not required to be equidistant). Here the random effects λ, ν and η and the noise ε are assumed to be independently, normally distributed with mean zero. Note that by using the formulations $\rho \exp(\nu_i)$ and $\gamma \exp(\eta_i)$ we accomplish that ρ_i and γ_i have lognormal prior distributions. Because of the experimental design and subject selection criteria of the data available to us, the state parameters ξ (prior homeostatic pressure for sleep) and φ (circadian phase) should be approximately identical for all subjects, and therefore no random effects are included for these.

Using $p[x;\mu,\sigma]$ to represent the normal probability density function with mean μ and variance σ^2 at x, the likelihood l_i of observing a given subject's samples y_i is proportional to:

$$l_i(y_i;\kappa,\lambda_i,\rho,\nu_i,\gamma,\eta_i,\xi,\varphi,\sigma) = h \prod_{j=0..m_i-1} p[y_{ij};P_{ij}(\kappa + \lambda_i,\rho \exp(\nu_i),\gamma \exp(\eta_i),\xi,\varphi),\sigma],$$

where σ represents the standard deviation of the noise ε_{ij}, h is a proportionality constant, and m_i is the number of data points contributed by subject i.

By integrating out the random effects λ, ν and η, each ranging from $-\infty$ to ∞, we get the marginal likelihood L_i:

$$L_i(y_i;\kappa,k,\rho,r,\gamma,c,\xi,\varphi,\sigma) = h' \iiint dk\, dr\, dc\, l_i(y_i;\kappa,\lambda_i,\rho,\nu_i,\gamma,\eta_i,\xi,\varphi,\sigma)\, p[\lambda_i;0,k]\, p[\nu_i;0,r]\, p[\eta_i;0,c],$$

where k, r and c represent the standard deviations of the random effects, and h' is a proportionality constant. Naturally, this expression can be rearranged to facilitate the numerical computation of the integrals.

The likelihood L of observing the entire set of samples y in the population data set is given by:

$$L(y;\kappa,k,\rho,r,\gamma,c,\xi,\varphi,\sigma) = h'' \prod_{i=0..n} L_i(y_i;\kappa,k,\rho,r,\gamma,c,\xi,\varphi,\sigma).$$

Here h'' is a proportionality constant.

Numerical estimation of the 9 parameters κ, k, ρ, r, γ, c, ξ, φ and σ establishes the population distribution model for performance, as per the two-process model, on which the Bayesian forecasting approach can be built.

Bayesian forecasting in the two-process model
Data are available from an AFOSR-sponsored 88-hour total sleep deprivation experiment conducted in our laboratory. The population distribution model for this data set is estimated by maximizing L, or rather minimizing $-2 \log L$, over the 9 parameters κ, k, ρ, r, γ, c, ξ, φ and σ. Using software designed especially for non-linear mixed-effects modeling (NONMEM), the following parameter estimates are found for this data set:
$\kappa = 30.3$, $k^2 = 36.7$, $\rho = 0.0283$, $r^2 = 1.67$, $\gamma = 4.35$, $c^2 = 0.372$, $\xi = -28.4$, $\varphi = 17.0$, and $\sigma^2 = 69.5$.

The crux of the Bayesian forecasting technique is that when a new subject who has not been studied before (arbitrarily indexed as $i = 0$) presents himself as an individual whose trait parameters we wish to estimate "on the fly" (i.e., as data y_{0j} for this subject become available one by one in real time), we can use the population distribution model to make specific predictions of this individual's future performance. Fixing κ, ρ, γ, ξ, φ and σ at their previously determined population values, the task is limited to estimating the subject's trait parameters λ_0, ν_0 and η_0 (i.e., a 3-parameter estimation problem). With Bayesian forecasting, the maximum likelihood estimates for λ_0, ν_0 and η_0 are those that minimize the following expression:

$$-l_0(y_0;\kappa,\lambda_0,\rho,\nu_0,\gamma,\eta_0,\xi,\varphi,\sigma)\, p[\lambda_0;0,k]\, p[\nu_0;0,r]\, p[\eta_0;0,c] \,/\, L_0(y_0;\kappa,k,\rho,r,\gamma,c,\xi,\varphi,\sigma).$$

A numerical algorithm to minimize this expression is currently being implemented.

Constructing a novel biomathematical model of fatigue and performance
Previously published biomathematical models of fatigue and performance have failed to predict the cumulative deficits resulting from chronic sleep restriction. To overcome this limitation, a

novel "slow" process modulating the setpoint of sleep/wake homeostasis over days has been proposed in the literature; this process will be referred to here as "process *U*". In support of specific aim 3, we integrated process *U* with the two-process model of sleep regulation.

The equations for process *S* in the two-process model have fixed upper and lower asymptotes (*U* and *L*), as can be seen when rewriting the published equations as follows:

$$S_t - U_t = (S_{t-\Delta t} - U_{t-\Delta t}) \exp(-\Delta t / \tau_r) \quad \text{during wake;}$$
$$S_t - L_t = (S_{t-\Delta t} - L_{t-\Delta t}) \exp(-\Delta t / \tau_d) \quad \text{during sleep;}$$

where $U_t = 1$ and $L_t = 0$ for all times t. We implemented process *U* by manipulating the asymptotes *U* and *L*, as follows:

$$U_t = U_{t-\Delta t} + M_w \Delta t \quad \text{during wake;}$$
$$U_t = U_{t-\Delta t} + (1 - U_{t-\Delta t})(1 - \exp(-M_s \Delta t)) \quad \text{during sleep;}$$
$$L_t = U_t - 1 \quad \text{during both wake and sleep.}$$

In these equations, M_w and M_s are rate parameters for process *U* during wake and sleep, respectively.

To estimate optimal values for these parameters, we derived a closed-form version of the set of equations for *S*, *U* and *L* given above. The closed-form equation set was derived for the conditions occurring in a series of laboratory experiments of chronic sleep restriction and total sleep deprivation conducted in our laboratory. The data from these experiments could thus be used to estimate the model parameters.

Assuming stable performance and sleep/wake patterns with 8 hours sleep in the week before the experiments (in agreement with actigraphy and diary data), we derived the initial values for *S*, *U* and *L* upon baseline awakening to be given by (where "h" indicates hours):

$$S_0 = U_0 - (1 - \exp(-8h / \tau_d)) / (1 - \exp(-16h / \tau_r - 8h / \tau_d));$$
$$U_0 = 1 + 16h\, M_w / (\exp(8h\, M_s) - 1);$$
$$L_0 = U_0 - 1;$$

where τ_d is a time constant from the original two-process model.

Model predictions thus computed were fitted to the experimental observations, using psychomotor vigilance performance lapses (reaction times $\geq$ 500 milliseconds) on a 10-minute psychomotor vigilance task (PVT) as the dependent variable. We used the observations from 2 baseline days (8 hours time in bed per day), 3 days of total sleep deprivation or 14 days of chronic sleep restriction (4, 6 or 8 hours time in bed per day) for a total of $n = 47$ subjects, as well as data from 1 recovery day (8 hours time in bed) for the subset of 34 subjects exposed to chronic sleep restriction. Observations were available every 2 hours during scheduled wakefulness; sleep inertia effects were excluded from the data set by removing data points collected immediately after awakening. On the basis of recently published findings regarding

sleep inertia from our laboratory, we also removed data points collected 2 hours after awakening for the subjects in the experimental condition with 4 hours time in bed per day.

The entire data set y_{it} (containing 5,443 data points) was subjected to mixed-effects regression against the biomathematical model predictions using the following equation:

$$y_{it} = a_i (S_t + \gamma C_t) + b_i + \varepsilon_{it}.$$

The circadian amplitude γ and circadian phase φ were designated free parameters, in order to allow for realignment of process C relative to process S as might be necessary due to the integration of process U. The rate constants M_w and M_s of process U were also designated free parameters. Independent, normally distributed random effects were included for linear scaling parameters a and b to account for inter-individual differences. Parameter assessment was performed with NONMEM.

The parameter estimates (± standard error) were $M_w = 0.553 \pm 0.788$ / h; $M_s = 0.0115 \pm 0.0040$ / h; $\gamma = 4.77 \pm 6.67$; $\varphi = 6.15 \pm 0.69$; $a = 0.305 \pm 0.427$; and $b = -24.5 \pm 10.5$. Comparison of the biomathematical model predictions with the experimental data revealed that the trends in psychomotor vigilance performance over days were accurately predicted for the conditions with 6 and 8 hours time in bed per day. However, performance impairment in the condition with 4 hours time in bed per day was overestimated, and performance impairment in the total sleep deprivation condition was underestimated. The relatively large standard errors for parameters M_w, γ and a also suggested that there is room for improvement. Even so, integration of process U in the two-process model yielded considerable improvement in the accuracy of performance predictions relative to the original two-process model.

Further work

The project is being continued at Washington State University, where we are exploring further improvements by modifying the shape of the circadian process C (which should also reduce the standard error for parameter γ); by changing the values of the parameters τ_r and τ_d of the homeostatic process S; and by using polysomnographically estimated total sleep time instead of time in bed as a basis for the model predictions. If these options do not yield significant further improvement, the less parsimonious possibility of modulating of the relationship between the upper and lower asymptotes U and L (presently fixed via $L_t = U_t - 1$) will also be investigated.

PERSONNEL SUPPORTED AND/OR ASSOCIATED WITH THE PROJECT

Hans P.A. Van Dongen, Ph.D. (PI)
David F. Dinges, Ph.D. (Co-PI)
Claire G. Fox (registered polysomnographic technologist)
Michele M. Carlin (study coordinator, data manager)
Oliver Crenshaw (IT specialist)
Deepa Avinash (Master's degree student)
Blair M. Robinson (undergraduate student)
Darshil D. Amin (undergraduate student)

PUBLICATIONS

D. Avinash, C.P. Crudele, D.D. Amin, B.M. Robinson, D.F. Dinges & H.P.A. Van Dongen (2005). Parameter estimation for a biomathematical model of psychomotor vigilance performance under laboratory conditions of chronic sleep restriction. *Sleep-Wake Research in The Netherlands* 16: 39–42.

H.P.A. Van Dongen, J.A. Caldwell & J.L. Caldwell (2006). Investigating systematic individual differences in sleep-deprived performance on a high-fidelity flight simulator. *Behavior Research Methods*, in press.

INTERACTIONS AND TRANSITIONS

Participation/presentations at meetings, conferences, seminars, etc. (Van Dongen)

03/2005 "Investigating the neurobehavioral consequences of sleep deprivation"
Washington State University, Pullman, WA

05/2005 "Mathematical models of neurobehavioral performance changes over time: Challenges and potential for use in scheduling tools"
Aerospace Medical Association 76th Annual Scientific Meeting, Kansas City, MO

06/2005 "Modeling human cognitive performance with the two-process model and beyond"
American Professional Sleep Societies 19th Annual Meeting, Denver, CO

06/2005 "Sleep loss: Individual differences and effects on routine life"
10th Annual Trainee Symposium, American Professional Sleep Societies 19th Annual Meeting, Denver, CO

09/2005 "Sleep loss and circadian stressors in shiftwork: On inter-individual differences"
Keynote lecture, 17th International Symposium on Shiftwork and Working Time, Hoofddorp, The Netherlands

09/2005 "Theoretical and mathematical predictions of the two-process model relative to sleep debt and excess wakefulness"
World Federation of Sleep Research and Sleep Medicine Societies Conference, New Delhi, India

Consultative and advisory functions to other laboratories and agencies (Van Dongen)

04/2005–05/2005 University of Pittsburgh School of Medicine (Dr. Peter Franzen)
Consultant (mixed-effects models) for NIH K23 Career Development Award

06/2005–03/2006 Walter Reed Army Institute of Research (Dr. Adam Fletcher)
Individual differences modeling of caffeine effects on cognitive performance

07/2005 U.S. Army Medical Research and Materiel Command & Defense Advanced Research Projects Agency (Dr. Michael Russo)
Academic liaison for pharmacologic countermeasures panel at military operational medicine workshop *Cognitive performance: Force multiplication through human-in-the-loop augmentation*, 19–21 July 2005, Las Vegas, NV

Transitions

Pulsar Inc. (Daniel Mollicone)

Transitioned the Bayesian forecasting framework developed as part of this grant (Specific Aim 1), so that Pulsar Inc. could initiate the development of a state/trait optimization tool deployable by the military for the prediction of cognitive performance in the face of both unknown individual traits and uncertain prior states. This has subsequently led to Phase I and Phase II SBIR contracts with the military.

THESES RESULTING FROM THE WORK

Ms. Deepa Avinash successfully defended her Master's thesis on a portion of the work performed for the present project, on 23 August 2005 at Drexel University, Philadelphia, PA. The executive summary of her thesis is as follows:

Laboratory experiments have demonstrated that cognitive performance deteriorates due to sleep deprivation and sleep restriction (even if sleep is reduced only a few hours per day on a chronic basis). Various biomathematical models have been developed to predict performance deficits resulting from sleep deprivation. One influential model is the "two-process model" of sleep regulation, which predicts sleep and performance on the basis of two interacting processes. The first process, referred to as the "sleep homeostat" or Process S, which seeks to balance time spent awake and time spent asleep. The second process, known as the "circadian rhythm" or Process C, is driven by the biological clock in the brain, which keeps track of the time of day. The two-process model properly predicts the performance degradation associated with multiple days of total sleep deprivation, but does not accurately predict performance under conditions of chronic partial sleep restriction. The model predicts that chronic sleep restriction leads to relatively little cognitive impairment, whereas laboratory experiments have shown that performance deteriorates progressively across days of sleep restriction. This thesis describes the development of an expansion of the two-process model to accurately predict the performance impairment resulting from chronic sleep loss, by integrating a novel Process U along with the original two processes S and C. The parameters of Process U were estimated using statistical analysis. The parameter assessment was performed by maximum likelihood estimation using nonlinear mixed effects modeling (NONMEM) software. The predictions of the expanded two-process model were compared to psychomotor vigilance task (PVT) performance data from a laboratory experiment involving 14 days of sleep restriction to 4 h, 6 h or 8 h time in bed (TIB) or 3 days of total sleep deprivation. Model predictions were fitted to experimental observations of PVT lapses (reaction times $\geq$ 500 ms), as measured every 2 h during scheduled wakefulness in the laboratory study. We used the observations from two baseline days (8 h TIB per day) and all experimental sleep loss days, for a total of $n = 47$ subjects; as well as data from one recovery day (8 h TIB) for the subset of 34 subjects exposed to chronic sleep restriction. The expanded two-process model may prove useful in operational environments faced with sleep loss, such as hospitals, emergency services, and transportation. The model could be used for improved scheduling of work hours for people working in such sleep-deprived environments, or to signal the need to employ fatigue countermeasures to maintain optimal performance. Thus the expanded model may help optimize safety and performance.